infection is associated with B lymphomas in immunosuppressed patients (Bennett et al., *Cecil Textbook of Medicine,* 20th ed., pp. 1776-1779, W.B. Saunders, Philadelphia Pa. (1996); Fauci et al., *Harrison's Principles of Internal Medicine,* 14th ed., pp. 1089-1091, McGraw-Hill, San Francisco Calif. (1998)).

[0011] Functional impairment of T cells is characteristic of many human viral infections (see Day et al., *Nature* 443: 350-354 (2006) and references cited therein). PD-1 is a negative regulator of activated T cells, and is markedly upregulated on the surface of exhausted virus-specific $CD8^+$ T cells (Ishida et al., *EMBO J.* 11:3887-3895 (1992); Noshimura et al., *Immunity* 11:141-151 (1999); Sharpe et al., *Nat. Rev. Immunol.* 2:116-126 (2002); Che, *Nat. Rev. Immunol.* 4:336-347 (2004); Barber et al., *Nature* 439:682-687 (2006)). Blockade of this pathway using antibodies against the PD ligand 1 (PD-L1, also known as CD274) restores $CD8^+$ T-cell function and reduces viral load (Barber et al., *Nature* 439:682-687 (2006)). It was found that PD-1 is significantly upregulated on T cells, and expression correlates with impaired HIV-specific $CD8^+$ T-cell function as well as predictors of disease progression: positively with plasma viral load and inversely with $CD4^+$ T-cell count (Day et al., *Nature* 443:350-354 (2006)). PD-1 expression on $CD4^+$ T cells likewise showed a positive correlation with viral load and an inverse correlation with $CD4^+$ T-cell count, and blockade of the pathway augmented HIV-specific $CD4^+$ and $CD8^+$ T-cell function (Day et al., *Nature* 443:350-354 (2006)). The results described by Day et al. (supra, 2006) indicate that the immunoregulatory PD-1/PD-L1 pathway is operative during a persistent viral infection in humans, and define a reversible defect in HIV-specific T-cell function (Day et al., *Nature* 443:350-354 (2006)).

[0012] PD-1-mediated inhibitory signaling not only attenuates HBV-specific $CD8^+$ T-cell effector function during the acute phase of infection but also correlates with the development of HBV-specific memory $CD8^+$ T cells following disease resolution (Zhang et al., *J. Hepatol.* 50:1163-1173 (2009)). In a study of patients with hepatitis B, PD-1 was significantly upregulated and subsequently led to the functional suppression of HBV-specific effector $CD8^+$ T cells, as blocking PD-1/PD-L1 interactions in vitro enhanced their proliferation and IFN-gamma production (Zhang et al., supra, 2009). Following disease resolution, HBV-specific effector $CD8^+$ T cells developed into memory T cells. During this period, the dynamic PD-1 decrease was numerically correlated with the reduction of HBV-specific $CD8^+$ T-cell frequency, phenotypically correlated with an acquisition of CCR7, CD45RA and CD127 expression, and functionally correlated with the increase in proliferation and IFN-gamma production of the memory T cells (Zhang et al., supra, 2009).

[0013] Chronic viral infection, unlike acute infection, leads to a large expansion of regulatory T cells (Treg cells) and their upregulation of PD-1 (Park et al., supra, *J. Immunol.* 194:5801-5811 (2015)). Treg cells from chronically infected mice (chronic Treg cells) displayed greater suppressive capacity for inhibiting both $CD8^+$ and $CD4^+$ T cell proliferation and for inhibiting subsequent cytokine production than those from naive or acutely infected mice (Park et al., supra, 2015). A contact between Treg and $CD8^+$ T cells was necessary for the potent suppression of $CD8^+$ T cell immune response. More importantly, the suppression required cell-specific expression and interaction of PD-1 on chronic Treg cells and PD-1 ligand on $CD8^+$ T cells (Park et al., supra, 2015).

[0014] T cell therapy has been previously described, in which the host immune system is utilized to treat or eliminate cancer or viral infections (see "T Cell Therapies: An Overview" Catapult Cell and Gene Therapy, White Paper 1 (ct.catapult.org.uk/wp-content/uploads/2016/03/Review-of-T-cell-Receptor-Therapies-2014_v2.pdf) (2014); Rooney et al., *Mol. Ther. Nucleic Acids* 1:e55, doi: 10.1038/mtna.2012.49 (2012)). Such therapies include gene modified T cell receptor (TCR) therapies and chimeric antigen receptor (CAR) therapies (see "T Cell Therapies: An Overview" Catapult Cell and Gene Therapy, White Paper 1 (ct.catapult.org.uk/wp-content/uploads/2016/03/Review-of-T-cell-Receptor-Therapies-2014_v2.pdf) (2014)). The use of CAR therapy in the treatment of conditions such as cancer has been previously described (see, for example, Sadelain et al., *Cancer Discov.* 3(4):388-398 (2013); Jensen et al., *Immunol. Rev.* 257:127-133 (2014); Sharpe et al., *Dis. Model Mech.* 8(4):337-350 (2015); Brentjens et al., *Clin. Cancer Res.* 13:5426-5435 (2007); Gade et al., *Cancer Res.* 65:9080-9088 (2005); Maher et al., *Nat. Biotechnol.* 20:70-75 (2002); Kershaw et al., *J. Immunol.* 173:2143-2150 (2004); Sadelain et al., *Curr. Opin. Immunol.* 21(2):215-223 (2009); Hollyman et al., *J. Immunother.* 32:169-180 (2009); WO/2015/188141).

[0015] There exists a need for therapies to provide improved treatment of viral infections, such as chronic viral infections. The object of the present invention is to satisfy this need.

5. SUMMARY OF INVENTION

[0016] The present invention relates to cells that are immune cells, which cells recombinantly express a dominant negative form of an inhibitor of a cell-mediated immune response of the immune cell, and optionally recombinantly express a chimeric antigen receptor (CAR), wherein the CAR binds to a viral antigen.

[0017] In one aspect, provided herein is a cell that is an immunostimulatory cell or precursor cell thereof, which cell recombinantly expresses (a) a chimeric antigen receptor (CAR), and (b) a dominant negative form of an inhibitor of a cell-mediated immune response of the immunostimulatory cell, wherein the CAR binds to a viral antigen. In another aspect, provided herein is a population of immunostimulatory cells or precursor cells thereof, which cell population comprises cells that recombinantly express (a) a chimeric antigen receptor (CAR), and (b) a dominant negative form of an inhibitor of a cell-mediated immune response of the immunostimulatory cell, wherein the CAR binds to a viral antigen. In certain embodiments, the immunostimulatory cell is a T cell. In certain embodiments, the precursor cell is a hematopoietic stem or hematopoietic progenitor cell. In a specific embodiment, the immunostimulatory cell is a cytotoxic T lymphocyte (CTL). In another specific embodiment, the cell is a T cell. In another specific embodiment, the cell is a Natural Killer (NK) cell. In another specific embodiment, the cell is a memory T cell. In another specific embodiment, the memory T cell is a memory $CD8^+$ T cell.

[0018] In another aspect, provided herein is a T cell that recognizes and is sensitized to a viral antigen, which T cell recombinantly expresses a dominant negative form of an inhibitor of a T cell-mediated immune response. In certain